CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-335

CORRESPONDENCE

Robert A. Miranda
Associate Director
Drug Regulatory
Affairs

Novartis Pharmaceuticals Corporation

Tel 973/781-2282
Fax 973/781-6325
internet: robert.miranda
@pharma.novardis.com

NOVARTIS

Fax

Attention: Ms. Ann Staten
FDA
Division of Oncologic Drug Products (HFD-150)
Rockville, MD

Fax no. 301/827-4590
Number of pages 1 including cover page

Date May 10, 2001

Concerning **NDA 21-335 Gleevec (imatinib mesylate capsules)**
RE: Additional Dissolution Agreement

Dear Ann,

Reference is made to my earlier fax today committing to the / minute dissolution specifications. As promised, I am providing batch numbers for the five lots tested and released under the minute specifications for US launch. These are as follows:

S 00100
S 00200
S 00300
S 00400
S 00500

We also commit to testing these five already approved batches using the new / -minute specification to generate data for your review.

Please contact me at 973/781-2282 if you have any questions or comments.

Sincerely yours,

Robert A. Miranda
Robert A. Miranda

Robert A. Miranda
Associate Director
Drug Regulatory
Affairs

Novartis Pharmaceuticals Corporation

Tel 973/781-2282
Fax 973/781-6325
Internet: robert.miranda
@pharma.novardis.com

NOVARTIS

Fax

Attention: Ms. Ann Staten
FDA
Division of Oncologic Drug Products (HFD-150)
Rockville, MD

Fax no. 301/827-4590
Number of pages 1 including cover page

Date May 10, 2001

Concerning **NDA 21-335 Gleevec (imatinib mesylate capsules)**
RE: Agreement

Dear Ann,

Reference is made to your faxes of May 10, 2001 containing the current PI and the Dissolution proposals. We agree with all of these.

The PI is acceptable.

We commit to the new dissolution spec of (minutes for new batches. We also understand that previous batches released under the NDA specification of (minutes will be acceptable. We agree to provide the batch numbers of all lots released under the (minute specification later today (about 5 batches). As we proceed with future commercial batches we will collect data both for the (and (minutes and submit this.

We also acknowledge your communication reflecting the fact that as we collect data (mins) we will share this data with the Division for evaluation with the intent to avoid any commercial shortages.

Sincerely yours,

Robert A. Miranda

Batches that are released under
(min. will be retested
at (minutes

Sincerely,

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachments

Desk Copy via fax: Ann Staten (HFD-150 at 301/827-4590)

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

Post-it® Fax Note 7671	Date 5/8/01	# of pages ▶ 6
To ANN STATEN	From R. MIRANDA	
Co./Dept.	Co.	
Phone #	Phone #	
Fax # 301/827-4590	Fax #	

May 8, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION

OTHER: PHASE 4 COMMITMENTS (Updated)

Dear Dr. Pazdur:

Please refer to our original NDA 21-335, dated February 27, 2001 for Gleevec™ (imatinib mesylate, formerly STI571, CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Reference is also made to a fax dated April 27, 2001and an e-mail dated May 8, 2001 from Ms. Ann Staten, which contained the Phase 4 commitments regarding this indication. At this time we would like to provide our agreement to comply with all of these commitments.

Each of the commitments mentioned in the referenced fax and e-mail are repeated below followed by our agreement.

I. ACCELERATED APPROVAL COMMITMENTS:

1. Please commit to conduct and submit the final study report for Protocol 106 entitled "A phase III study of STI571 versus Interferon-α (IFN-α) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)" with Time to Progression (TTP) as the primary surrogate endpoint. TTP is defined as any of the following:
   -Loss of CHR
   -Loss of cytogenetic response
   -Inability to maintain peripheral blood counts
   -Increasing organomegaly
   -Accelerated phase CML
   -Blast crisis
   -Death from CML

Response: We commit to conducting and submitting the final study report for Protocol 106. This study is currently ongoing and the interim analysis (one-year hematologic response and QoL) is planned for 1Q02 and the final analysis is expected in 4Q05.

2. Please commit to provide us with interval follow-up information on studies 102, 109 and 110.

   Response: We commit to providing a safety and efficacy update for these studies in July 2001, with a final analysis report expected in 3Q01.

II. REGULAR PHASE 4 COMMITMENTS:

1. Conduct and submit final study reports for pediatrics studies (study 0103- a phase I study in children with refractory/relapsed Ph+ leukemias and a phase 2 efficacy study conducted in an appropriate pediatric population.)

   Response:

   a) We commit to conducting and submitting the final study report for Study 0103. This study is currently ongoing and being conducted by the cooperative group COG (Children's Oncology Group). A final report is expected at the end of the year or 1Q02.

   b) In addition, a phase 2 pediatric efficacy study is planned to start after completion of the phase 1 Study 0103. This will be conducted by a pediatric cooperative group under the NCI. We will submit the draft protocol for your review within 2 months after the approval of this NDA. Study initiation is planned about 2 months later and the final report is planned to be submitted within 12 months after approval.

2. Conduct and submit final study reports for hepatotoxic drug interactions (such as acetaminophen, etc.)

   Response: We commit to conducting the appropriate study to assess hepatotoxic drug interactions (e.g. acetaminophen). We will submit the draft protocol for your review within 4 months after the approval of this NDA. Study initiation is planned about 2 months later and the final report is planned to be submitted in 1Q2002.

3. Conduct and submit an *in vivo* study of drug interactions mediated by CYP2D6 .

   Response: This was a repeat of #5 below. Please see our response for item #5

4. Implement a physician and patient education program regarding use of concomitant medications with STI571 (CYP 3A4 and 2D6 interactions).

   Response: We commit to implement a physician and patient education program regarding the use of concomitant medications with Gleevec. We propose to include educational language in our product monograph, patient brochure and the Gleevec.com website. We will submit our proposals for your review prior to implementation within 2 months after this NDA approval.

5. In vitro studies suggest that both STI571 and its major active metabolite are potent inhibitors of CYP 2D6 isoenzyme. The impact of CYP2D6 inhibition by STI 571 on the pharmacokinetics of drugs, which are substrates of CYP 2D6, is unknown. Currently, no dosage recommendation can be made for patients who will be taking drugs, which are substrates of CYP 2D6. Therefore, you should assess potential drug interaction between imatinib and a substrate of CYP2D6. Please submit your study protocol for review.

   Response: We commit to conducting the appropriate study to assess the potential drug interaction between imatinib and a substrate of CYP2D6. We will submit the draft protocol for your review within 3 months after the approval of this NDA. Study initiation is planned about 2 months later, and the final report is planned to be submitted in 1Q2002.

6. Gleevec is predominantly metabolized and eliminated through the biliary route. Since there is no clinical study conducted with Gleevec in patients with liver impairment, no specific advice regarding dosing adjustment can be given to patients with liver function insufficiency. Therefore, you should conduct a pharmacokinetics study with Gleevec in subjects or patients with liver impairment. Please submit your study protocol for review.

   Response: We commit to conducting a PK study with Gleevec in subjects or patients with liver impairment. We are currently working with NCI to conduct such a study and a draft study protocol will be submitted for your review within 3 months after the approval of this NDA. Study initiation is planned about 2 months later and the final report is planned to be submitted within 18 months after approval.

7. The contribution of the major metabolite of STI 571, N-demethylated piperazine derivative, in the overall pharmacologic or toxic effect of Gleevec could not be assessed. Although the AUC of the major metabolite was 16% of the parent drug, low plasma protein binding of this metabolite could potentially play a role in the overall pharmacologic or toxic effect of Gleevec. Therefore, you should assess the plasma protein binding of the N-demethylated piperazine derivative of STI571.

   Response: We commit to conducting an appropriate study to assess the plasma protein binding of the major Gleevec metabolite (N-demethylated piperazine). We will submit the draft protocol for your review within 2 months after the approval of this NDA. Study initiation is planned about two months later and the final report is planned to be submitted within 6 months after approval.

8. Evaluate the etiology and treatment of the fluid retention syndrome associated with imatinib treatment and meet with the Division of Oncology within 2 months of the approval to discuss your plans.

   Response: We agree.

If you have any questions or comments regarding this matter, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Desk Copy via fax: Ann Staten (HFD-150 at 301/827-4590)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	5/8/01
TELEPHONE NO. (*Include Area Code*)	FACSIMILE (FAX) Number (*Include Area Code*)
(973) 781-2282	(973) 781-6325
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*):	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
59 Route 10 East Hanover, New Jersey 07936-1080	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (*If previously issued*) 21-335

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
imatinib mesylate	Gleevec™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
	ST1571, CGP57148B

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsules	50 and 100 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
chronic myeloid leukemia (CML)

APPLICATION INFORMATION

APPLICATION TYPE (*check one*)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (*check one*) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
PHASE 4 COMMITMENTS

PROPOSED MARKETING STATUS (*check one*) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)* Phase 4 Commitments

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert A Miranda	Robert A. Miranda, Associate Director Drug Regulatory Affairs	5/8/01

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
59 Route 10 East Hanover, New Jersey 07936-1080	(973) 781-2282

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Electronic Mail Message

Date: 5/7/01 4:27:23 PM
From: Ann Staten (STATENA)
To: leslie.martinhischak (leslie.martinhischak@pharma.Novartis.com)
Subject: Gleevec - PK comments

Dear Leslie,
Here are 2 comments from the PK reviewr.

1. The dissolution specifications are set as follows.

Dissolution conditions:

Apparatus: Basket method (Apparatus 1)
Speed: 100 rpm
Test medium: 0.1 N hydrochloric acid
Volume: 1000 mL
Temperature: 37 ± 0.5 °C

Q value not less than 80 % of the declared content dissolved in 15 minutes.

2.

Please call me with any questions.

Sincerely,

ann

/S/

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler	**From:** Dianne Spillman
Fax: (301) 468-5614	**Fax:** (301) 594-0499
Phone: (301) 468-5602	**Phone:** (301) 594-5746
Pages (including cover): 27	**Date:** May 2, 2000
Re: IND \FDA bullets & overheads	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Ellen:

As promised, here are the Division's internal bullets (13 pages) and the overheads (13 pages) that may be presented by Drs. John Johnson & Marty Cohen prior to discussion of the internal bullets. Please distribute copies of this fax to the attendees on your end.

At the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request.

Sincerely,

S

Dianne Spillman, Project Manager
Division of Oncology Drug Products

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

May 1, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION

OTHER: REVISED BOTTLE LABELS

Dear Dr. Pazdur:

Please refer to our original NDA 21-335, dated February 27, 2001 for Gleevec™ (imatinib mesylate, formerly STI571, CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Reference is also made to a fax dated April 20, 2001 from Ms. Ann Staten, which included CMC review comments, including one bottle label comment. At this time we would like to submit revised bottle labels to address the one CMC comment and reflect the new tradename approved on April 17, 2001.

Attached are the revised bottle labels for the following Gleevec bottles:

- 50mg, 30 capsule bottle
- 100mg, 100 capsule bottle
- 100mg, 120 capsule bottle
- 100mg, 180 capsule bottle

These bottle labels now contain the new tradename Gleevec (previously ( )). In accordance with the CMC review comment we have also added the statement "Each capsule contains 50 [or 100] mg of imatinib free base".

If you have any questions or comments regarding this matter, please contact me at (973) 781-2282.

6 pages redacted from this section of the approval package consisted of draft labeling

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

DUPLICATE

April 30, 2001

NEW CORRESP
NC

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

Draft Promotional Materials (Part 4)
(Accelerated NDA Review)

Dear Dr. Pazdur:

Reference is made to our original NDA 21-335, dated February 27, 2001 for Gleevec™ (imatinib mesylate, formerly STI571 and CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

As you know, this NDA is being reviewed under the accelerated approval regulations. At this time we would like to provide copies of our phase 2 website to be used during the first 120 days of the post-approval period, in accordance to 21 CFR 314.550. Our previous submissions of draft promotional materials were done on April 23, 25 and 26, 2001.

We have listed the enclosed draft phase 2 website in order of preference by the groups identified in our previous submission.

Group #1 (highest priority):
None at this time

Group #2 (medium priority):
1. **www.gleevec.com website (Phase 2)**

Group #3 (lower priority):
None at this time

The following is a brief description of the draft promotional piece enclosed:

Website (phase 2) – www.gleevec.com (5 sheets):

As previously mentioned in an earlier submission, we intend to roll out the Gleevec.com website in phases as submitted materials are approved for use on the site. Phase 1 (submitted April 26, 2001) is targeted to go live on the day of FDA approval. Phase 1 will include an announcement of the approval of Gleevec™ (imatinib mesylate), as well as information on Gleevec reimbursement services for patients and prescribers of Gleevec. Phase 1 will also include an opt-in e-mail collection function, so that interested parties may request to be updated when new information is posted on Gleevec.com. This form will ask the requester some additional non-required questions to help guide us in appropriately targeting updates to the website in the future.

The final look (called Phase 2) of the Gleevec.com website (enclosed) will be derived from pre-approved content already submitted. Website content will be categorized as content for Healthcare Professionals, or Patients and Caregivers, and website visitors will be directed as such through the site navigation.

Previous visitors, who have requested to be informed when Gleevec.com is updated, will receive two waves of emails, dependent upon the receipt of DDMAC review on previously submitted pieces. Content will be updated as approved pieces are added to the site to expedite the availability of approved information.

This current submission of the Phase 2 (final) website consists of the following:

- E-mails for website visitors who have requested to be informed of Gleevec.com updates.
- Updated website homepage with healthcare and patient sections added.
- Example of the patient secondary page. The healthcare secondary page will be similar and contain one of the other similar graphics (patient photos) taken from the patient brochure.
- Description of the above two sections and their contents. Most contents are previously submitted pieces and are specifically identified.

This concludes our draft promotional submissions under the accelerated approval regulations, 21 CFR 314.550.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

RAM:vh
attachments

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Bob Miranda, Novartis
Fax:

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 2

Date: 4-30-01

COMMENTS: Re: your pending NDA for STI571, we have the following requests:

Please make two additional changes to the draft label:

1. DRAFT LABELING

2.

Please edit the adverse reactions table:

1. In addition to the summary numbers for fluid retention, provide separate reporting of a superficial edema category and a category to include effusions, ascites and pulmonary edema.

2. Combine pain in the abdomen with pain in the upper abdomen.

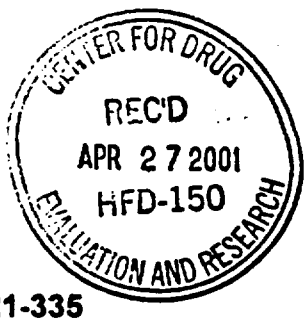
APPEARS THIS WAY
ON ORIGINAL

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

ORIGINAL



April 26, 2001

NEW CORRESP
NC

NDA No. 21-335

GLEEVEC ™ (imatinib mesylate) Capsules

Draft Promotional Materials (Part 3)
(Accelerated NDA Review)

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Pazdur:

Reference is made to our original NDA 21-335, dated February 27, 2001 for Gleevec™ (imatinib mesylate, formerly STI571 and CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

As you know, this NDA is being reviewed under the accelerated approval regulations. At this time we would like to provide copies of our phase 1 website to be used on the first day of approval, in accordance to 21 CFR 314.550. Our previous submissions of draft promotional materials were done on April 23 and 25, 2001.

To facilitate your review, all promotional pieces are referenced as appropriate to the master collection of references previously submitted on April 23, 2001 as necessary. Specific text ~~in the~~ references is highlighted or specifically identified by document, page, column and paragraph.

We have listed the enclosed draft website in order of preference by groups and within groups to facilitate our needs, if possible. These groups are consistent with those identified in our previous submission.

Group #1:
1. www.gleevec.com website (Phase 1)
2. Pharm Alert

Group #2:
None at this time

Group #3:
None at this time

The following is a brief description of each draft promotional piece enclosed:

Website – ww.gleevec.com (7 sheets):

We intend to roll out the Gleevec.com website in phases as previously submitted materials are approved. Phase 1 (enclosed) is targeted to go live on the day of FDA approval. Phase 1 will include an announcement of the approval of Gleevec™ (imatinib mesylate), as well as information on Gleevec reimbursement services for patients and prescribers of Gleevec. Phase 1 will also include an opt-in e-mail collection function, so that interested parties may request to be updated when new information is posted on Gleevec.com. This form will ask the requester some additional non-required questions to help guide us in appropriately targeting updates to the website in the future.

The final look (called Phase 2) of the Gleevec.com website will be derived from pre-approved content already submitted. Website content will be categorized as content for Healthcare Professionals or Patients and Caregivers and website visitors will be directed as such through the sites navigation.

This Phase 2 is being developed and will be submitted for review shortly.

Pharm Alert (4 sheets):

The Pharm Alert will be direct mailed to retail pharmacists and oncology nurses. Approved full prescribing information will be included. A color annotated copy of this letter is enclosed.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda

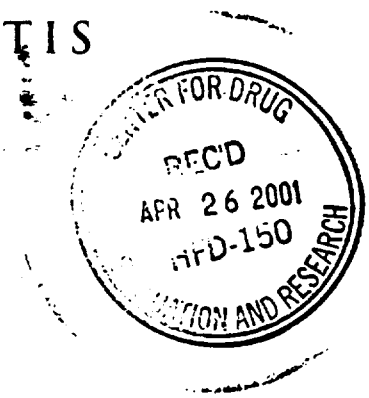
Robert A. Miranda
Associate Director
Drug Regulatory Affairs

RAM:vh
attachments

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS



ORIGINAL

April 25, 2001

NDA No. 21-335

GLEEVEC ™ (imatinib mesylate) Capsules

Draft Promotional Materials (Part 2)
(Accelerated NDA Review)

NC

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Pazdur:

Reference is made to our original NDA 21-335, dated February 27, 2001 for Gleevec™ (imatinib mesylate, formerly STI571 and CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. As you know, this NDA is being reviewed under the accelerated approval regulations. At this time we would like to provide copies of additional draft promotional materials to be used during the first 120-day postapproval period, in accordance to 21 CFR 314.550. Our first submission of draft promotional materials was done on April 23, 2001.

This submission was prepared in accordance with the FDA guidance to industry entitled "Accelerated Approval Products – Submission of Promotional Materials". For your convenience, we have enclosed a copy of the draft package insert submitted to the original NDA. We are submitting one copy of the attached materials to your Division and two copies have been sent directly to DDMAC.

To facilitate your review, all promotional pieces are referenced as appropriate to the master collection of references previously submitted on April 23, 2001. Specific text in the references is highlighted or specifically identified by document, page, column and paragraph.

We have listed the enclosed draft promotional materials below in order of preference by groups and within groups to facilitate our needs, if possible. These groups are consistent with those identified in our previous submission.

Group #1:
None submitted at this time for this high priority group. The website, which will belong to this group, is being prepared and will be submitted before April 30th.

Group #2:
1. Formulary Kit – Housing, Tabs and Bibliography List

Group #3:
1. Mail Research Study
2. Gleevec Slide Kit
3. Mechanism of Action (MOA) CD ROM

The following is a brief description of each draft promotional piece enclosed:

Formulary Kit – Housing, Tabs and Bibliography List (26 sheets):

The formulary kit will include prescribing information, monograph*, reprints of the NEJM CML articles*, AHFS fact sheet*, and bibliography. These materials will be on a CDROM as read only files. Color copies of the housing unit, CD ROM label copy, tab sheets and bibliography list are enclosed. Content will also be posted on gleevec.com internet site within the MD/health care professional segment.

*Previously submitted for review under separate cover.

Mail Research Study (10 sheets):

The mail research study is a market research initiative, which will be direct mailed to healthcare professionals. Annotated color copies of the research direct mail are enclosed.

Gleevec Slide Kit (20 sheets)
The slide kit will be distributed by Novartis Oncology sales specialists. Annotated copies of the slide kit are enclosed. Content will also be posted on gleevec.com internet site within the MD/health care professional segment.

MOA CD ROM (3 sheets plus CD ROM):
The Mechanism of Action (MOA) CD ROM will be distributed by Novartis Oncology sales specialists and at conventions. A copy of the CD ROM and packaging are enclosed. Content will also be posted on gleevec.com internet site within the MD/health care professional segment.

This submission consists of one loose-leaf volume.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

RAM:vh
enclosures

Desk Copy (2): Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
(HFD-42)
5600 Fishers Lane
Rockville, Maryland 20857
Attention: Joseph A. Grillo

Desk Copy (letter only): A. Staten, HFD-150 (via fax 301/827-4590)

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

ORIGINAL

April 23, 2001

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

NDA No. 21-335

GLEEVEC ™ (imatinib mesylate) Capsules

Draft Promotional Materials
(Accelerated NDA Review)

NEW CORRESP
NC

Dear Dr. Pazdur:

Reference is made to our original NDA 21-335, dated February 27, 2001 for Gleevec™ (imatinib mesylate, formerly STI571 and CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. As you know, this NDA is being reviewed under the accelerated approval regulations. At this time we would like to provide copies of draft promotional materials to be used during the first 120-day postapproval period, in accordance to 21 CFR 314.550.

This submission was prepared in accordance with the FDA guidance to industry entitled "Accelerated Approval Products – Submission of Promotional Materials". For your convenience, we have enclosed a copy of the draft package insert submitted to the original NDA. We are submitting one copy of the attached materials to your Division and two copies have been sent directly to DDMAC.

To facilitate your review, all promotional pieces are referenced as appropriate. These references are provided in a single master collection of references in two separate loose leaf binders. Specific text in the references is highlighted

The following draft promotional materials are enclosed for your review and represent most of our promotional launch campaign intended for use during the first 120 days following marketing approval. Additional promotional materials (about six pieces) are pending and will be submitted to you by April 30, 2001.

We have listed the enclosed draft promotional materials below in order of preference by groups and within groups to facilitate our needs, if possible.

Group #1:
1. Now Available and Coming Soon ASCO Panels
2. AHFS Fact Sheet
3. Hem/Onc Mailing
4. OTN Fax
5. Rolodex Card
6. Patient brochure
7. Patient Brief Summary
8. Medical Necessity Letter and Holder
9. Detail Aid
10. Journal Ad
11. Professional Brief Summary
12. Product Monograph

Group #2:
1. Now Available Journal Ad
2. Tabletop Panels

Group #3:
1. Launch Waves 1-4 Check Study

The following is a brief description of each draft promotional piece enclosed:

Now Available and Coming Soon Panels (2 sheets):

The "Now Available" Panel will be displayed at convention exhibits after approval (specifically ASCO 2001). Approved prescribing information will be available at the exhibit booth for Healthcare professionals. If Gleevec is not approved before ASCO 2001, the "Coming Soon" panel will be displayed.

AHFS Fact Sheet (2 sheets):

The AHFS Fact Sheet will be distributed at conventions and by Novartis Oncology sales representatives and business relation managers and is intended to be left with physicians, pharmacists, payers, and wholesalers. In addition, the fact sheet is to be included in the Formulary Kit. Content for the sheet adheres to the established AHFS guidelines. The approved prescribing information will be enclosed in a pocket in the piece.

Hem/Onc Mailing (3 sheets):

The Hem/Onc Mailing will be mailed to Healthcare professionals (i.e. hematologists, oncologists, and oncology nurses) upon approval of Gleevec. The mailing will include the approved prescribing information and a rolodex card (see below for description). The letter will be printed on Novartis Oncology letterhead.

OTN Fax (1 sheet):

The OTN Fax will be sent via fax to hematologists and oncologists upon approval. The fax will be accompanied by the approved prescribing information.

Rolodex Card (1 sheet):

The Rolodex Card will be distributed at conventions, in mailings, and by Novartis Oncology sales representatives. The card provides customers with the reimbursement hotline for Gleevec.

Patient Brochure (13 sheets):

The patient brochure will be distributed to Healthcare professionals and support groups, as well as distributed directly to patients. The brochure will include the patient brief summary (see below). Content will also be posted on gleevec.com internet site within the patient segment.

Patient Brief Summary (1 sheet):

The patient brief summary will be included in patient materials, including the patient journal ad and patient brochure. The brief summary was created in accordance with available guidelines.

Medical Necessity Letter and Holder (5 sheets):

The medical necessity letter and cover sheet will be distributed by Novartis Oncology sales specialists to physicians. Content will also be posted on gleevec.com internet site within the MD/health care professional segment.

Detail Aid (4 sheets) and slim jim version:

The sales detail aid is for use by Novartis Oncology sales representatives and is not intended to be left with physicians. The inside back page pocket will contain the approved package insert. Content will also be posted on gleevec.com internet site within the MD/health care professional segment.

Note: After approval of the sales aid, we will create a 'slim jim' (9" x 4") version – an exact duplicate of the sales aid, in a smaller size. The slim jim sales aid will be used by Novartis Oncology sales representatives and will be left with Healthcare professionals. In addition, it will be distributed at conventions. The slim jim will include the approved prescribing information in a pocket (as noted in the sales aid as well).

Journal Ad (2 sheets):

The journal ad will be placed in professional journals. The last page of the journal ad will include the professional brief summary (see below).

Professional Brief Summary (1 sheet):

The professional brief summary will accompany the professional journal ad unit. The brief summary was developed in accordance with established guidelines.

Product Monograph (23 sheets):

The monograph will be distributed to Healthcare professionals by Novartis Oncology sales specialists and business relations managers, available through Novartis Medical Services and at conventions. It will also be included in the formulary kit (see below). Color copies of the monograph are enclosed. Content will also be posted on gleevec.com internet site within the MD/health care professional segment.

Now Available Journal Ad (1 sheet):

The "Now Available" journal ad will be included in professional medical journals.

Table Top Panels (1 sheet):

The "Now Available" table top panels will be used by Novartis Oncology sales specialists when displaying approved product material at local/community exhibits.

Launch Mail Waves 1-4 (12 sheets):

Launch mail waves will be direct mailed to hematologists, oncologists and oncology nurses. Approved full prescribing information will be included with each wave mail. Slide kit will be distributed by Novartis Oncology sales specialists. Annotated copies of the slide kit are enclosed. Content will also be posted on gleevec.com internet site within the MD/health care professional segment.

This submission consists of three loose-leaf volumes.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

NOVARTIS

VENA T. HERALD
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10, Bldg. 419/1251
East Hanover, New Jersey

Tel: (973) 781-5403
Fax: (973) 781-6325

facsimile transmittal

To:	Ann Staten	**Fax:**	(301) 827-4590
Co:	FDA HFD-150		
From:	**Vena T. Herald** for Robert Miranda vena.herald@pharma.novartis.com	**Date:**	April 10, 2001
Re:	NDA No. 21-335 ™ MINOR AMENDMENT TO A PENDING APPLICATION NEW TRADE MARK	**Pages:**	4 pages including cover

☐ **Urgent** ☐ **For Review** ☐ **As Requested** ☐ **Please Reply**

** If this transmission is incomplete please contact Vena Herald @ (973) 781-5403.*

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

April 16, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

(imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION

OTHER: NEW TRADEMARK

Dear Dr. Pazdur:

Please refer to our original NDA 21-335, dated February 27, 2001 for (imatinib mesylate, formerly STI571, CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Reference is also made to a fax dated April 2, 2001 from Ms. Ann Staten, which included the OPDRA review comments as reasons why the trademark is not acceptable and our. The main reason given was because of the phonetic similarities between and GLYSET. The trademark was originally submitted for review to our IND on July 26, 2000 (Serial No. 089).

At this time we would like to provide additional information that may not have been available to OPDRA when it did its risk benefit analysis. We believe that this information supports the use of our preferred trademark

We ask for your expedited consideration of this information. We recognize the accelerated review assigned to this NDA and the potential importance to patients for this drug. As such we appreciate your immediate attention to this issue to avoid any potential delay in providing the product to patients in a timely fashion immediately after approval.

An international interdisciplinary group from Novartis has carefully reviewed the OPDRA evaluation, along with two error potential evaluations performed by Med-ERRS, a subsidiary of the Institute for Safe Medication Practices (ISMP). The first of the Med-ERRS evaluations was completed on March 23, 2001 and supported the Novartis decision to adopt as the trademark for imatinib mesylate. The second Med-ERRS evaluation was completed on April 4, 2001 in response to the OPDRA evaluation that surfaced a concern about GLYSET. This second evaluation was a Failure Mode and Effects Analysis of versus GLYSET and continues to support the use of the trademark

Based on the information from the two Med-ERRS evaluations (attached) and for other reasons, we believe the trademark ( ) is a low risk for confusion with GLYSET. This summarized in the following six topic areas:

Distribution of( )

Novartis will ship supplies of ( )in a controlled manner. There will be no automatic shipments of( ) made to retail pharmacies. For a variety of reasons, among them a relatively small chronic myeloid leukemia (CML) patient population of approximately 23,000 individuals, Novartis has identified a number of select wholesalers that have the technical capability and resources to provide patient-specific delivery service to retail pharmacies on an as needed basis. These wholesalers will maintain inventories of( )and will provide adequate patient service at the retail level without the need for retail pharmacies to maintain shelf inventories of( ) Consequently, we believe that the absence of shelf inventories of( )at the retail level essentially eliminates the potential for confusion with GLYSET, a product that is not widely used in the management of diabetes. The reported new prescriptions written for GLYSET is very low and is reported at about an average of)per month since its launch in Feb 1999.

Visual Distinctions between( )and GLYSET

A visual comparison between( )and GLYSET shows a number of distinctions between the two products that should reduce the likelihood of confusion at the pharmacy and patient level. GLYSET is available as 25 mg, 50 mg and 100 mg white, round, film-coated tablets. These tablets are debossed with the word "Glyset" on one side and the strength on the other side( )will be marketed as a light yellow to orange yellow opaque capsule in a 100 mg strength, with an imprinted alpha-numeric code. These visual distinctions should allow patients to immediately identify any differences during prescription refills.

Low Risk Potential for( )d GLYSET Confusion

As described in the second Med-ERRS Failure Mode and Effects Analysis (attached), there is a low risk of confusion between( )nd GLYSET that could lead to medication errors. This report is based on a detailed, side by side comparison of the two products that tracked them from the wholesaler, pharmacy storage, prescribing physician, techniques for prescribing, order entry at the pharmacy, selection of product at pharmacy, dispensing, and finally patient administration. At each step in this eight-step sequence, the report describes a "low risk of confusion", with the exception of pharmacy storage, where the risk of confusion was described as "moderate". The controlled distribution procedures described above further reduce this moderate risk in practice.

Medical Differences

The dose and administration guidelines will also serve to minimize confusion. The usual maintenance dose of GLYSET is 50 mg 3 times daily, with a maximum recommended dose of 100 mg 3 times daily. ( )will be prescribed for chronic phase CML as 400 mg (4 capsules) given once daily, for advanced phase CML 600 mg (6 capsules) given once daily.

Pronunciation and Verbal Orders

In the first Med-ERRS evaluation (attached), all 37 pharmacist respondents were given the Novartis pronunciation (GLEE-VEK), and none of them mentioned GLYSET as a potential problem with a verbal order. US practitioners did point out that without specific instructions the tendency was to pronounce ( ) with the long "i" sound, as it would sound with a "GLY" prefix. However, based on the second Med-ERRS Failure Mode and Effects Analysis, we believe the risk is low for creating confusion that would lead to medication errors. To further reduce any potential risk we also plan to include a pronunciation guide in our educational programs.

Public Awareness

The extensive exchange of information within the media (print & TV) concerning ( ) over the past four months, and particularly in the most recent period surrounding the publication of our Phase I studies in the New England Journal of Medicine, many health practitioners and CML patients are aware of ( ) as a promising new treatment for the selected indications. This awareness translates to extraordinary name recognition, and this should further reduce the likelihood of prescription-writing or dispensing errors at launch and beyond. Finally, reference is made to over 630 million references made over the last four months surrounding the use ( ) plus CML patient internet sites which have prominently featured this trademark (e.g. newcmldrug.com).

In the unlikely event that there is confusion with GLYSET and the risk of medication errors, in the post-launch period, Novartis is willing to work with the Agency in a cooperative way to carefully monitor the situation and immediately implement interventions so as to manage the risks in a manner acceptable to the Agency.

Because of the shared urgency on this matter, we respectfully request a conference call on or before April 16, 2001(p.m.) or April 17, 2001 (a.m.) to discuss the contents of this letter and the attachments. We are enclosing six copies of the information package so that you can more easily share the information with OPDRA and others in a timely manner. Please let me know if you need additional copies.

If you have any questions or comments regarding this matter, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachments

Desk Copy via fax: Ann Staten (HFD-150 at 301/827-4590)
cc: Jerry Phillips (OPDRA)

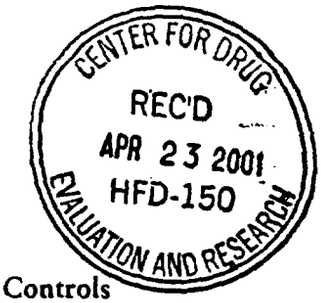
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

April 19, 2001

DUPLICATE



NDA 21-335
(imatinib mesylate)
Capsules

DRUG AMENDMENT
BC

Minor Amendment to a Pending NDA- Chemistry, Manufacturing and Controls
FDA Information Request

Richard Pazdur, MD
Director
Division of Oncology Drug Products, HFD-150
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Pazdur:

Please refer to the above cited Original NDA for (imatinib mesylate) Capsules which was submitted on 27-FEB-01. This amendment provides for the removal of Novartis, East Hanover, NJ as a site to perform stability testing. Please note that the East Hanover Site was inadvertently included in the original NDA and should be removed. All other site information is correct and current.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact Ms. Leslie Martin-Hischak directly at (973) 781-3758. If there are any general or Clinical related issues please contact Mr. Robert A. Miranda, the DRA Therapeutic Area representative at (973) 781-2282.

Sincerely,

Robert J. Clark
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

cc: Ms. Regina Brown, New Jersey District Office, North Brunswick
Resident Post - Certified Field Copy (Cover Letter Only)